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The role of vulnerability factors in individuals with an at-risk mental state of psychosis

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Abstract

Background: Several indicators of heightened vulnerability to psychosis and relevant stressors have been identified. However, it has rarely been studied prospectively to what extent these vulnerability factors are in fact more frequently present in individuals with an at-risk mental state for psychosis. Moreover, it remains unknown whether any of these contribute to the prediction of psychosis onset in at-risk mental state individuals.

Methods: Twenty-eight healthy controls, 86 first-episode psychosis patients and 127 at-risk mental state individuals were recruited within the Basel 'Früherkennung von Psychosen' project. Relative frequencies of selected vulnerability factors for psychosis were compared between healthy controls, psychosis patients, those at-risk mental state individuals with subsequent psychosis onset (n = 31) and those without subsequent psychosis onset (n = 55). Survival analyses were applied to determine associations between time to transition to psychosis and vulnerability factors in all 127 at-risk mental state individuals.

Results: The vulnerability factors/indicators "difficulties during school education or vocational training", "difficulties during employment", "being single", "difficulties with intimate relationships", and "being burdened with specific stressful situations" were more commonly found in the at-risk mental state and first-episode psychosis group than in healthy controls.

Conclusions: At-risk mental state and first-episode psychosis individuals more frequently present with vulnerability factors. Individual vulnerability factors appear, however, not to be predictive for an onset of psychosis.

Zusammenfassung

Hintergrund: Verschiedene Indikatoren für eine erhöhte Vulnerabilität für Psychosen und relevante Stressoren sind identifiziert worden. Bislang wurde jedoch nicht ausreichend untersucht, ob diese Vulnerabilitätsfaktoren auch häufiger bei Personen mit einem Risikostatus für eine Psychose und ersterkrankten Psychose-Patienten vorliegen. Zudem ist unklar, ob sie zur Prädiktion einer psychotischen Dekompensation bei Personen mit einem Psychoserisiko-Status beitragen.

Methoden: Achtundzwanzig gesunde Kontrollen, 86 ersterkrankte Psychose-Patienten und 127 Personen mit einem Psychoserisiko-Status wurden innerhalb des Basler 'Früherkennung von Psychosen' Projektes rekrutiert. Die relativen Häufigkeiten ausgewählter Vulnerabilitätsfaktoren für Psychose wurden zwischen gesunden Kontrollen, Psychose-Patienten, jenen Risikopatienten mit späterer Psychose-Entwicklung (n = 31) und jenen ohne Psychose-Entwicklung (n=55) verglichen. Survival-Analysen wurden verwendet, um Assoziationen zwischen der Zeit bis zu einer psychotischen Dekompensation und Vulnerabilitätsfaktoren in allen 127 Probanden mit Psychoserisiko-Status zu bestimmen.

Ergebnisse: Die Vulnerabilitätsfaktoren/indikatoren „Schwierigkeiten während der Schul- oder Berufsausbildung", „Schwierigkeiten während der Arbeit", „alleinstehend sein", „Schwierigkeiten bei intimen Beziehungen" und „sich belastet fühlen durch stressige Situationen", waren häufiger bei den Psychoserisiko-Patienten und den ersterkrankten Psychose-Patienten vorhanden als bei gesunden Kontrollen.

Schlussfolgerungen: Psychoserisiko-Patienten und ersterkrankte Psychose-Patienten weisen häufiger Vulnerabilitätsfaktoren/indikatoren auf. Einzeln scheinen diese jedoch nicht prädiktiv für eine psychotische Dekompensation zu sein.

Background

Schizophrenic psychoses are aetiologically complex diseases that affect about 0.5-1% of the population during their lifetime [1]. Family, twin and adoption studies have consistently suggested a strong genetic component to the aetiology of schizophrenic psychoses, while the effects of environmental factors on the emergence of psychoses have been typically found to be rather modest [2]. However, it has been argued that heritability measures may underestimate the role of environmental factors since complex gene-environment interplay mechanisms are included in the genetic component of the heritability model [2]. Accordingly, major attempts are currently being undertaken to gain deeper insights into the complex ways in which genetic and environmental factors interact to provoke psychoses [3].

As suggested by Zubin and Spring [4] in their vulnerability-stress model of schizophrenia, internal and external stressors interact with the neurobiological proneness of an individual, thereby triggering the onset of illness. Identifying indicators of heightened vulnerability for psychoses and relevant stressors may thus have important consequences to our understanding of the aetiology of these disorders. Indicators of vulnerability are presumed to reflect on-going proneness to develop psychoses and refer to anomalous traits that are already present prior to the onset of clinical symptoms [5]. As such, they are considered more central to underlying aetiological processes than the clinical symptoms themselves [5]. Stressors such as discrete life events or prevailing stress have been shown to influence the onset and course of schizophrenic psychoses [6].

Here, we collectively refer to vulnerability indicators and stressors as vulnerability factors since it is not possible to distinguish whether these factors are early or late indicators of increased vulnerability, a consequence of the early stages of disease development or external stressors in the sense of triggers.

Over the past decades, several vulnerability factors for the development of psychoses have been identified. For the prenatal period until birth, in utero infections, malnutrition, advanced paternal age, maternal stress, birth during winter and early spring, and non-specific complications during pregnancy and delivery have repeatedly been shown to be associated with an increased risk for schizophrenic psychoses [7]. The most replicated vulnerability factors for psychoses include urban upbringing, migration, cannabis use, low socio-economic status, childhood trauma and infections [7].

How these vulnerability factors contribute to the risk for psychoses is subject to intense debate. For instance, it has been hypothesized that urban upbringing may be linked to psychoses via the mediating effect of various other factors related to urban living. These include greater exposure to toxins, increased health risk behaviours such as smoking or drug abuse, increased stress, distinct dietary patterns, and specific sociocultural features [8].

The majority of research on vulnerability factors for psychoses has been conducted retrospectively in individuals already affected by the disease. By contrast, less research has examined these factors in at-risk mental state (ARMS) individuals who are suspected to be in the prodromal phase of psychosis or first-episode psychosis (FEP) patients [9]. Given that the effects of stressors may be even more pronounced prior or during the first onset of psychosis [10], it appears vital to study vulnerability factors in

ARMS and FEP individuals. Moreover, this approach may help to determine preventive strategies to counteract an onset of psychosis.

Previous studies in ARMS or FEP individuals observed higher proportions of various vulnerability factors in these study groups as compared to healthy controls (HC), suggesting that they may play a role in the onset of psychoses [11]. Among these, difficulties during school education [12-15] or employment [16, 17], being single [18, 16], difficulties in intimate relationships [19], motor coordination difficulties during childhood [20], substance abuse [21], and a close family history of psychiatric disorders [16] have been identified. Moreover, being more commonly exposed to stressful situations such as feeling criticised by others [22] has been associated with an ARMS or psychosis.

In this study, we compared the relative frequencies of the aforementioned vulnerability factors for psychoses between ARMS, FEP and HC individuals and investigated their contribution to transition to psychosis. We hypothesized that vulnerability factors associated with psychoses are more prevalent in FEP and ARMS individuals than in HC subjects. Moreover, we assumed that they are associated with transition to psychoses in ARMS individuals.

Methods

Setting and recruitment

Study participants were recruited between 01/03/2000 and 31/07/2014 as part of the prospective "*F*rüh*e*rkennung von *Psy*chosen" (*FePsy*; English: early detection of psychosis) study. A detailed description of the study design can be found elsewhere [23]. In brief, individuals suspected to be in their early (prodromal) phase of psychosis were referred to our specialised early detection clinic at the Psychiatric University Outpatient Department of the Psychiatric University Clinics Basel, Switzerland. HC subjects were recruited from trade schools, hospital staff and through advertisements.

To be included into the study, individuals had to be at least 18 years of age. Exclusion criteria for FEP and ARMS individuals were as follows: insufficient knowledge of German, IQ below 70, previous episode of schizophrenic psychosis, psychosis clearly due to organic reasons or substance abuse, or psychotic symptomatology within a clearly diagnosed affective psychosis or borderline personality disorder. Subjects treated with antipsychotics > 3 weeks or who had exceeded a 2500mg cumulative chlorpromazine equivalent dose were excluded. For the HC group, a current or former psychiatric disorder or neurological disease, serious medical condition, substance abuse, or a family history of psychiatric disorders were additional exclusion criteria.

This study was approved by the regional Ethics Committee (EKNZ) and conforms to the provisions of the Declaration of Helsinki. All participants provided written informed consent.

Screening procedure

Individuals were screened with the Basel Screening Instrument for Psychosis (BSIP) which has been specifically designed for identifying individuals presenting with putative prodromal symptoms or full-blown (first-episode) psychosis [24]. The BSIP consists of seven sections that capture prodromal symptoms as specified in the revised third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) [25], other early psychosis symptoms as derived from the literature, and current or previous (pre)psychotic symptoms corresponding to the Personal Assessment and Crisis Evaluation (PACE) criteria [26]. Individuals were classified as being in an ARMS if they met one of the following inclusion criteria: (a) attenuated or brief limited psychotic symptoms according to the PACE criteria [26]; (b) familial aggregation of psychotic disorders in combination with at least two further risk factors similar to the PACE criteria [26]; or (c) a minimal amount and combination of certain risk factors according to screening instrument (for details, see [24]). The BSIP has been shown to have a good interrater reliability ($\kappa = 0.67$) for the assessment of the main outcome category "at-risk for psychosis" and a high predictive validity [24].

On the basis of the BSIP, individuals were classified as either being in an ARMS for psychosis, having an established (first-episode) psychosis, or being not at increased risk of psychosis. ARMS and FEP individuals were invited to take part in the FePsy study, provided that they did not meet any exclusion criteria as outlined above.

Assessment of vulnerability factors

Following study inclusion, all participants were assessed using the Basel Interview for Psychosis (BIP) [27]. The BIP is a comprehensive semi-structured interview specifically designed for assessing the development of psychopathological symptoms and the presence of psychosis vulnerability indicators and stressors. For this study, items from the first section of the BIP "social and physical development, family" and the third section "vulnerability" were selected.

In the first section of the BIP, items are measured on a binary scale indicating the presence or absence of a given vulnerability factor. Here, the following vulnerability indicators and stressors were selected (Table 1): (a) difficulties during school or vocational training resulting in repetition of a class, interruption, drop out or change; (b) difficulties during employment resulting in interruption, drop out or change; (c) a marital status of being single, separated, divorced or widowed; (d) exceptional difficulties in relationships with partners; (e) motor coordination difficulties during childhood; and (f) lifetime substance use. As described before, individuals fulfilling criteria for current drug use (except cannabis) were excluded from this study.

In the third section of the BIP, items are measures on a three-point ordinal scale corresponding to vulnerability indicators either being "present", "questionable present" or "not present". For the current analysis, only items coded as being "present" or "not present" were considered. The following vulnerability indicators were selected (Table 1): (a) being burdened with criticism or rejection by others; (b) being burdened with conflicts with others; (c) being burdened with intensive positive feelings towards others;

(d) being burdened with ambiguous situations; (e) being burdened with noisy environments, (f) being burdened with working under time pressure.

In the following we collectively refer to vulnerability indicators and stressors as "vulnerability factors".

[Table 1 about here]

Follow-up and transition to psychosis

ARMS individuals were re-assessed at regular time intervals to examine whether transition to psychosis had occurred. Transition to psychosis was examined based on the Brief Psychiatric Rating Scale (BPRS) [28] items "suspiciousness", "unusual thought content", "hallucinations" and "conceptual disorganization" which are implemented in the BSIP and correspond to the criteria by Yung et al. [26]. To disentangle the impact of vulnerability factors on transition to psychosis, the ARMS group was divided post hoc into those who experienced no transition to psychosis during the follow-up period (ARMS-NT) and those with a transition to psychosis (ARMS-T).

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 22.0. A p-value of $\leq .05$ was considered statistically significant. Differences in socio-demographic characteristics between the diagnostic

groups (HC, ARMS-NT, ARMS-T, FEP) were examined using Analyses of Variance (ANOVA) or Chi^2-tests where appropriate.

To investigate whether significant differences between HC, ARMS-NT, ARMS-T and FEP regarding vulnerability factors exist, we compared the selected items of the BIP between the groups using the Chi^2-test. In case of significant findings, post-hoc Chi^2-tests were employed to compare two groups each with each other. For this comparison, only ARMS-NT subjects with a follow-up duration of at least three years were included in the analysis in order to reduce the likelihood that these individuals may still go on to develop psychosis.

Since some of the outcome measures contained missing data, we performed multiple imputations using SPSS for study participants that provided information for at least half of the outcome measures of interest. Here, we generated 100 imputations of the missing values such that 100 completed datasets were obtained to protect against a potential power falloff from a too small number of imputations [29]. For study participants who provided less than half of the BIP outcome measures of interest, no imputations of missing values were conducted and non-existing values were considered missing.

Next, survival analyses were conducted to examine the predictive value of the selected vulnerability factors for transition to psychosis (event) in the ARMS group. Here, the whole ARMS-NT sample regardless of their follow-up duration were included in the analysis since survival analyses take this factor into account. The Cox proportional hazards regression model was applied to each variable to test for the association between a particular variable and later transition to psychosis, taking into account the time to transition to psychosis. Age and gender served as covariates in our model.

Results

Sample characteristics

In total, 241 individuals were recruited as part of the *FePsy* study during the specified time interval that provided information for at least one of the vulnerability factors of interest and were thus included in this study. These were 28 HC (12%), 86 FEP (36%) and 127 ARMS (53%) individuals. In total, 31 ARMS individuals had a transition to psychosis during the follow-up period (ARMS-T), while 96 did not (ARMS-NT). Fifty-five of the latter were regarded as "true" non-converters because we had followed them up for at least three years (median follow-up duration: 60 months), while the remaining ARMS-NT had been followed-up for a shorter period of time (median follow-up duration: 10 months).

For five individuals (2.1%), more than half of the BIP items were missing. Accordingly, no imputations of missing items for these individuals were conducted. All other subjects provided information for at least half of the BIP items and missing values were thus imputed (for details, see Supplementary Table 1).

With regard to socio-demographic characteristics (Table 2), there were no significant differences between the groups in terms of gender or psychotherapeutic treatments. However, age and years of education significantly differed between the groups. Post-hoc analyses showed that the HC group was significantly younger than the FEP group ($p = 0.001$) and had completed significantly more years of education as compared to the ARMS-NT ($p = 0.014$), ARMS-T ($p = 0.010$) and FEP ($p = 0.010$) groups. Finally, there were significant differences between the groups regarding current pharmacotherapy and current severity of psychiatric symptoms. Post-hoc analyses showed that the FEP group, as expected, received more frequently antipsychotic

medication at baseline as compared to ARMS-NT (p = 0.001) and ARMS-T individuals (p = 0.001) and more frequently antidepressant medication at baseline as compared to ARMS-NT individuals (p = 0.012). Also, the FEP group had significantly more severe psychiatric symptoms as compared to both ARMS groups (both p = 0.001). Between the ARMS-NT and ARMS-T groups, no significant socio-demographic differences emerged (Table 3).

[Tables 2 and 3 about here]

Frequency of vulnerability factors between the groups

When comparing the proportion of the selected vulnerability factors between the groups, several significant differences emerged (Table 4). First of all, there was a significant group effect for the vulnerability factors "difficulties during educational or occupational training" and "difficulties during employment". Post-hoc analyses revealed that the HC group had significantly less often difficulties during educational or vocational training as compared to the ARMS-NT (p = 0.001), ARMS-T (p = 0.001) and FEP (p = 0.001) group. Similarly, the HC group had significantly less often difficulties during employment than ARMS-NT (p = 0.006), ARMS-T (p = 0.001) and FEP (p = 0.001) individuals.

[Table 4 about here]

Moreover, significant differences between the groups emerged for “marital status”. Post-hoc analyses showed that the HC individuals were significantly less often single (including divorced, separated, widowed) than ARMS-NT ($p = 0.021$), ARMS-T ($p = 0.029$) and FEP ($p = 0.002$) subjects. Also, significant group differences emerged regarding “difficulties in relationships with partners”. The HC group had significantly less commonly difficulties in relationships with partners than ARMS-NT ($p = 0.004$), ARMS-T ($p = 0.013$) and FEP ($p = 0.001$) individuals.

Finally, significant differences between the groups emerged with regard to “being burdened with intense positive feelings towards others”, “being burdened with noisy environments” and “working under time pressure”. Post-hoc analyses revealed that the HC group was significantly less often burdened with intense positive feelings towards others as compared to the ARMS-NT ($p = 0.032$) and FEP group ($p = 0.005$). Moreover, HC individuals suffered significantly less often from noisy environments as compared to ARMS-NT ($p = 0.025$), ARMS-T ($p = 0.023$) and FEP ($p = 0.001$) subjects. The FEP group also suffered significantly more often from noisy environments as compared to the ARMS-T group ($p = 0.014$). With regard to working under time pressure, HC participants reported significantly less often being burdened with this stressor as compared to the ARMS-NT ($p = 0.002$), ARMS-T ($p = 0.001$) and the FEP ($p = 0.001$) groups.

Vulnerability factors as predictors of transition to psychosis

To investigate if any of these vulnerability factors predict transition to psychosis, we conducted survival analyses within the ARMS group ($n = 127$; Table 5). The analyses

revealed no significant association between time to transition to psychosis and any of the included vulnerability factors.

[Table 5 about here]

Discussion

In this study, we confirmed that a variety of vulnerability factors/indicators are more commonly present in individuals with an ARMS for psychosis and in FEP patients as compared to HC subjects. These include difficulties during school education or vocational training, difficulties during employment, being single, difficulties with intimate relationships, and being burdened with specific stressful situations. However, we did not find any of these vulnerability factors to carry a predictive value for a subsequent transition to psychosis on its own.

Our finding that difficulties during school education or vocational training and during employment are more common in ARMS-NT, ARMS-T and FEP individuals as compared to HC subjects is well in line with previous studies [12-15]. Given that widespread neurocognitive deficits have been detected in ARMS and FEP individuals [30, 31], it appears likely that these may negatively impact on school and work performance, leading to increased rates of interruption, drop out or change of school/employment in ARMS and FEP individuals. In line with this hypothesis, previous studies have indeed repeatedly observed an association between neurocognitive abilities and functional outcome, including occupational functioning [32].

The finding of our study that ARMS-NT, ARMS-T and FEP individuals are more likely to be single (including being separated, divorced, or widowed) as compared to the HC group is well in line with previous findings [16, 18]. Of note, being single appears to be particularly associated with an onset of psychosis in individuals living in areas with relatively few single people [33]. Interestingly, ARMS-NT, ARMS-T and FEP

individuals also reported more often difficulties in intimate relationships with partners than HC subjects which may reflect social functioning impairments that have been identified as a vulnerability factor for psychosis [34]. All in all, it appears likely that being single and having difficulties in intimate relationships are related to each other.

We found ARMS-NT and FEP individuals to feel more often burdened with intense positive feelings towards others as compared to controls. Moreover, being burdened with noisy environments and working under time pressure was significantly more common in ARMS-NT, ARMS-T and FEP individuals. These findings are in line with oversensitivity being an important first sign of emerging psychosis. They are also supporting the assumption that daily hassles can trigger the emergence of psychiatric symptoms via increased psychosocial stress [4], and in accordance with previous studies that observed daily stressors to be related to symptom severity in patients with schizophrenia [35] or individuals at risk for psychosis [36].

Although we observed various vulnerability factors to be more common in the ARMS and FEP groups, none of these factors was predictive for a subsequent transition to psychosis in ARMS individuals on its own. This finding does not exclude that these vulnerability factors are predictive in combination with each other or with other factors, which will be tested in a next step. Apart from that many vulnerability factors for psychosis appear to constitute general risk markers for a great variety of psychiatric disorders [37].

Our finding that difficulties during school education and employment are more common in both ARMS groups and FEP individuals but not predictive for an onset of psychosis is partly opposed to findings by Dragt et al. [38] who observed the frequency of job

change or interruption of school attendance to be associated with an onset of psychosis. One potential reason for this discrepancy may be related to the fact that the ARMS participants in the study of Dragt et al. [38] were on average about five years younger than those in our study cohort and had an earlier age of psychosis onset, with research indicating that early psychotic episodes are more likely preceded by environmental stressors than later episodes [39].

Previous research found a history of substance use to be predictive for transition to psychosis [40]. We did not find this vulnerability factor to be associated with an onset of psychosis in our study sample. Since a history of drug use was evident in more than 70% of our ARMS group, it would be interesting to assess the frequency and quantity for each type of drug in future follow-up appointments of the participants to determine whether these factors may impact on transition to psychosis.

Our findings imply that psychotherapeutic intervention programmes should focus on coping strategies to reduce the impact of stress in ARMS and FEP individuals. Amongst these, difficulties during school education or during employment, difficulties with intimate relationships and being exposed to specific stressful situations may be important aspects to consider. Moreover, help from social workers with school- or work-related problems may be beneficial as well as training in social skills where required.

The major strengths of this study are that we recruited a relatively large cohort of ARMS and FEP individuals and that ARMS individuals were followed up at regular intervals for a relatively long time period to assess transition to psychosis. Several limitations need to be addressed, though. First of all, interpretation of our results

regarding vulnerability factors for transition to psychosis needs to be conducted within the framework of the ARMS for psychosis since this study is not based on a general population sample but on help-seeking individuals presenting with putative prodromal symptoms. Furthermore we have so far only tested single factors regarding predictivity, not a combination of factors as indicators of underlying vulnerability. Second, the presence of vulnerability factors/indicators was only assessed at study intake and we can therefore not draw any conclusions regarding their course over time. Third, we did not assess the presence of protective factors such as coping skills in ARMS individuals which may have counteracted transition to psychosis. Fourth, ARMS individuals were examined regularly at our early detection clinic and received cognitive-behavioural case-management where needed. Accordingly, it appears likely that the support offered by the early detection clinic counteracted the influence of vulnerability factors on transition to psychosis. Fifth, as described in the introduction, it cannot be inferred from our data whether the observed vulnerability factors are indicators of increased vulnerability, a consequence of the early stages of disease development or external stressors in the sense of triggers.

In conclusion, ARMS and FEP individuals frequently present with various vulnerability factors, including difficulties during school education or vocational training, difficulties during employment, being single, difficulties with intimate relationships, and being burdened with specific stressful situations. Future research should assess vulnerability factors as well as protective factors in ARMS in more detail and study their interplay with other factors including genes to gain more insights into the pathophysiological mechanisms underlying the onset of clinical symptoms and full-blown psychosis.

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References

1. McGrath J, Saha S, Welham J, El Saadi O, MacCauley C, Chant D. A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. BMC Med 2004;2:13.
2. van Os J, Rutten BP, Poulton R. Gene-environment interactions in schizophrenia: review of epidemiological findings and future directions. Schizophr Bull 2008;34(6):1066-1082.
3. van Os J, Kenis G, Rutten BP. The environment and schizophrenia. Nature 2010;468(7321):203-212.
4. Zubin J, Spring B. Vulnerability--a new view of schizophrenia. J Abnorm Psychol 1977;86(2):103-126.
5. Nuechterlein KH, Dawson ME, Ventura J, Gitlin M, Subotnik KL, Snyder KS et al. The vulnerability/stress model of schizophrenic relapse: a longitudinal study. Acta Psychiatr Scand 1994;382:58-64.
6. Myin-Germeys I, van Os J. Stress-reactivity in psychosis: evidence for an affective pathway to psychosis. Clin Psychol Rev 2007;27(4):409-424.
7. Brown AS. The environment and susceptibility to schizophrenia. Prog Neurobiol 2011;93(1):23-58.
8. Cannon M, Clarke MC. Risk for schizophrenia--broadening the concepts, pushing back the boundaries. Schizophr Res 2005;79(1):5-13.
9. European Network of National Networks studying Gene-Environment Interactions in Schizophrenia. Identifying gene-environment interactions in schizophrenia: contemporary challenges for integrated, large-scale investigations. Schizophr Bull 2014;40(4):729-736.
10. Pruessner M, Iyer SN, Faridi K, Joober R, Malla AK. Stress and protective factors in individuals at ultra-high risk for psychosis, first episode psychosis and healthy controls. Schizophr Res 2011;129(1):29-35.
11. Riecher-Rössler A, Gschwandtner U, Borgwardt S, Aston J, Pflüger M, Rössler W. Early detection and treatment of schizophrenia: how early? Acta Psychiatr Scand 2006(429):73-80.
12. Addington J, Penn D, Woods SW, Addington D, Perkins DO. Social functioning in individuals at clinical high risk for psychosis. Schizophr Res 2008;99(1-3):119-124.

13. Ballon JS, Kaur T, Marks, II, Cadenhead KS. Social functioning in young people at risk for schizophrenia. Psychiatry Res 2007;151(1-2):29-35.
14. Lencz T, Smith CW, Auther A, Correll CU, Cornblatt B. Nonspecific and attenuated negative symptoms in patients at clinical high-risk for schizophrenia. Schizophr Res 2004;68(1):37-48.
15. Isohanni I, Jarvelin MR, Nieminen P, Jones P, Rantakallio P, Jokelainen J et al. School performance as a predictor of psychiatric hospitalization in adult life. A 28-year follow-up in the Northern Finland 1966 Birth Cohort. Psychol Med 1998;28(4):967-974.
16. Byrne M, Agerbo E, Eaton WW, Mortensen PB. Parental socio-economic status and risk of first admission with schizophrenia- a Danish national register based study. Soc Psych Psych Epid 2004;39(2):87-96.
17. Hui C, Morcillo C, Russo DA, Stochl J, Shelley GF, Painter M et al. Psychiatric morbidity, functioning and quality of life in young people at clinical high risk for psychosis. Schizophr Res 2013;148(1-3):175-180.
18. Kirkbride JB, Stochl J, Zimbron J, Crane CM, Metastasio A, Aguilar E et al. Social and spatial heterogeneity in psychosis proneness in a multilevel case-prodrome-control study. Acta Psychiatr Scand 2015; 132(4):283-292.
19. Ben-David S, Birnbaum ML, Eilenberg ME, DeVylder JE, Gill KE, Schienle J et al. The subjective experience of youths at clinically high risk of psychosis: a qualitative study. Psychiatr Serv 2014;65(12):1499-1501.
20. Niemi LT, Suvisaari JM, Tuulio-Henriksson A, Lonnqvist JK. Childhood developmental abnormalities in schizophrenia: evidence from high-risk studies. Schizophr Res 2003;60(2-3):239-258.
21. Murray RM, Grech A, Philips P, Johnson S. The relationship between substance abuse and schizophrenia. In: Murray R JP, Susser E, van Os J, Cannon M (Hrsg.). The Epidemiology of Schizophrenia. Cambridge, UK: Cambridge University Press; 2003. pp. 317-342.
22. Morrison AP, French P, Lewis SW, Roberts M, Raja S, Neil ST et al. Psychological factors in people at ultra-high risk of psychosis: comparisons with non-patients and associations with symptoms. Psychol Med 2006;36(10):1395-1404.

23. Riecher-Rössler A, Gschwandtner U, Aston J, Borgwardt S, Drewe M, Fuhr P et al. The Basel early-detection-of-psychosis (FEPSY)-study--design and preliminary results. Acta Psychiatr Scand 2007;115(2):114-125.
24. Riecher-Rössler A, Aston J, Ventura J, Merlo M, Borgwardt S, Gschwandtner U et al. [The Basel Screening Instrument for Psychosis (BSIP): development, structure, reliability and validity]. Fortschr Neurol Psychiatr 2008;76(4):207-216.
25. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders DSM-III-R. 3 ed. Washington, DC: American Psychiatric Association; 1987.
26. Yung AR, Phillips LJ, McGorry PD, McFarlane CA, Francey S, Harrigan S et al. Prediction of psychosis. A step towards indicated prevention of schizophrenia. Br J Psychiatry 1998;172(33):14-20.
27. Riecher-Rössler A, Ackermann T, Uttinger M, Ittig S, Koranyi S, Rapp C et al. [The Basel Interview for Psychosis (BIP): structure, reliability and validity]. Fortschr Neurol Psychiatr 2015;83(2):99-108.
28. Lukoff D, Nuechterlein KH, Ventura J. Manual for the expanded brief psychiatric rating scale. Schizophr Bull 1986;12:594–602.
29. Graham JW, Olchowski AE, Gilreath TD. How many imputations are really needed? Some practical clarifications of multiple imputation theory. Prev Sci 2007;8(3):206-213.
30. Bora E, Murray RM. Meta-analysis of cognitive deficits in ultra-high risk to psychosis and first-episode psychosis: do the cognitive deficits progress over, or after, the onset of psychosis? Schizophr Bull 2014;40(4):744-755.
31. Pflueger MO, Gschwandtner U, Stieglitz RD, Riecher-Rössler A. Neuropsychological deficits in individuals with an at risk mental state for psychosis - working memory as a potential trait marker. Schizophr Res 2007;97(1-3):14-24.
32. Rajji TK, Miranda D, Mulsant BH. Cognition, function, and disability in patients with schizophrenia: a review of longitudinal studies. Can J Psychiatry 2014;59(1):13-17.
33. van Os J, Driessen G, Gunther N, Delespaul P. Neighbourhood variation in incidence of schizophrenia. Evidence for person-environment interaction. Br J Psychiatry 2000;176:243-248.

34. Cornblatt BA, Carrion RE, Addington J, Seidman L, Walker EF, Cannon TD et al. Risk factors for psychosis: impaired social and role functioning. Schizophr Bull 2012;38(6):1247-1257.
35. Norman RM, Malla AK. A prospective study of daily stressors and symptomatology in schizophrenic patients. Soc Psych Psych Epid 1994;29(6):244-249.
36. Tessner KD, Mittal V, Walker EF. Longitudinal study of stressful life events and daily stressors among adolescents at high risk for psychotic disorders. Schizophr Bull 2011;37(2):432-441.
37. Cannon M, Caspi A, Moffitt TE, Harrington H, Taylor A, Murray RM et al. Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: results from a longitudinal birth cohort. Arch Gen Psychiatry 2002;59(5):449-456.
38. Dragt S, Nieman DH, Veltman D, Becker HE, van de Fliert R, de Haan L et al. Environmental factors and social adjustment as predictors of a first psychosis in subjects at ultra high risk. Schizophr Res 2011;125(1):69-76.
39. Castine MR, Meador-Woodruff JH, Dalack GW. The role of life events in onset and recurrent episodes of schizophrenia and schizoaffective disorder. J Psychiatr Res 1998;32(5):283-288.
40. Cannon TD, Cadenhead K, Cornblatt B, Woods SW, Addington J, Walker E et al. Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. Arch Gen Psychiatry 2008;65(1):28-37.

Table 1. Vulnerability factors as derived from Basel Interview for Psychosis (BIP)

	Corresponding items of Basel Interview for Psychosis (BIP)	
Vulnerability factor	**Item no.**	**Item wording**
Difficulties during school or vocational training	1.1.2 1.1.3a 1.2.2a	Have you ever had to repeat a class at school? Have you ever interrupted, dropped out of or changed school due to difficulties? Have you ever interrupted, dropped out of or changed vocational training due to difficulties?
Difficulties during employment	1.3.2a	Have you ever interrupted, dropped out of or changed employment due to difficulties?
Marital status of being single (including being separated, divorced, widowed)	1.4.1a	How about your current marital status?
Relationship difficulties with partners	1.4.4a	Have relationships with partners caused exceptional difficulties to you so far?
Separated from parent(s) when growing up	1.5.4a	When you were a child (until age of 12 years), did you always live together with both parents?
Motor coordination difficulties during childhood	1.6.7 1.6.8	During your childhood, have you ever been diagnosed with motor coordination difficulties (clumsiness of movements)? Did your mother ever say that you learned how to walk tardily?
Lifetime drug use	1.7.1a	Have you every consumed drugs?
Burdened with criticism or rejection	3.1	Do you feel burdened with criticism or rejection by others?
Burdened with conflicts	3.2	Do you feel burdened with conflicts with others?
Burdened with intense positive feelings	3.3	Do you also feel burdened with intense positive feelings towards others (affection, infatuation)?
Burdened with ambiguous situations	3.4	Do you feel burdened with ambiguous situations where you just do not know what you are dealing with?
Burdened with noisy environment	3.5	Do you feel burdened with having a conversation in a noisy environment or when there is much ambient noise?
Burdened with working under time pressure	3.6	Do you feel burdened when having to work under time pressure?